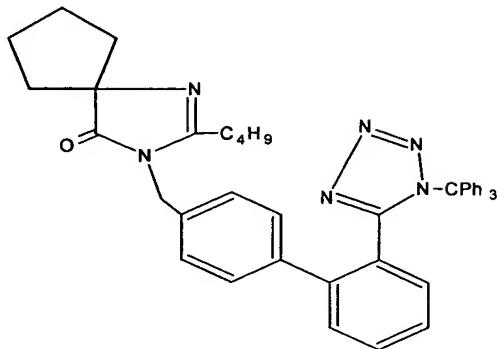


We claim

1. A process of making a compound of structure I

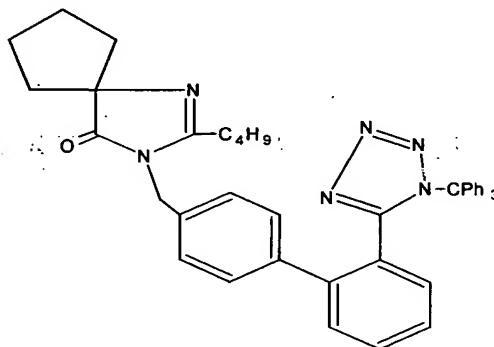


5 comprising the steps of:

- a) reacting 1(N'-pentanoylamino)cyclopentanecarboxylic acid amide with 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole in the presence of an inorganic base, a solvent and a phase transfer catalyst;
- b) cooling the mixture;
- 10 c) adding water to the mixture whereby two phases are obtained;
- d) separating the two phases obtained; and
- e) recovering the compound of structure I.

2. The process of claim 1, wherein the inorganic base is selected from the group consisting of alkali metal hydroxides, alkali metal carbonates or mixtures thereof.
- 15 3. The process of claim 2, wherein the alkali metal hydroxides are NaOH or KOH, and the alkali metal carbonate is K₂CO₃.
4. The process of claim 2, wherein the inorganic base is a mixture of bases and is used as a solid.
5. The process of claim 1, wherein the organic solvent is an aliphatic ether having up to 20 8 carbon atoms or an aromatic hydrocarbon.

6. The process of claim 5, wherein the aliphatic ether is methyl *t*-butyl ether or tetrahydrofuran.
7. The process of claim 5, wherein the aromatic hydrocarbon is toluene.
8. The process of claim 1, wherein the phase transfer catalyst is selected from the group consisting of quaternary ammonium compounds and phosphonium compounds.
- 5
9. The process of claim 8, wherein the phase transfer catalyst is tetrabutylammonium hydrogensulfate.
10. The process of claim 1, wherein the reacting is at a temperature from about 80°C to reflux.
- 10
11. The process of claim 10, wherein the reacting is at a temperature of about 90°C.
12. A process of making a compound of structure I



comprising the steps of:

- a) reacting, for a period of time of about 2 to about 24 hours, a valerimidate derivative with a first amine in the presence of a first acid and an organic solvent to form a mixture ;
- 15
- b) cooling the mixture;
- c) combining the mixture with a second amine and a catalytic amount of a second acid ;
- d) heating the combination at reflux for about 2 to about 24 hours;
- 20
- e) contacting the combination with a base whereby two phases are obtained;

- f) separating the phases obtained; and
- g) recovering the compound of structure I.

13. The process of claim 12 wherein the valerimidate derivative is a valerimidate ether, a valerimidate ester, or a salt of a valerimidate ester.

5 14. The process of claim 13, wherein said valerimidate derivative is selected from the group consisting of the methyl, ethyl, propyl, butyl, benzyl, pentyl and aryl valerimidate esters or salts thereof.

15. The process of claim 14, wherein said valerimidate derivative is ethyl valerimidate.

16. The process of claim 12, wherein the first and second amines are selected from the group consisting of 5'-(4'aminomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole and 1-aminocyclopentane carboxylic acid ethyl ester, with the proviso that first and second amines are not the same.

15 17. The process of claim 16, wherein the valerimidate derivative of step a is ethyl valerimidate methanesulfonic acid salt, the first amine is 5'-(4'aminomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole whereby N-valerimidate 5'-(4'aminomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole is formed in the combination.

18. The process of claim 16, wherein the valerimidate derivative of step a is ethyl valerimidate methanesulfonic acid salt, the first amine is 1-aminocyclopentane carboxylic acid ethyl ester whereby N-valerimidate-1-aminocyclopentane carboxylic acid ethyl ester is formed in the combination.

20 19. The process of claim 12, wherein the organic solvent is selected from the group consisting of N,N dimethyl formamide (DMF), dimethyl acetamide (DMA), toluene, hexane, 1,2-dimethoxyethane (DME), diethoxymethane, tetrahydrofuran (THF), benzene, m-xylene, o-xylene, tetralins, formals, glymes and mixtures thereof.

25 20. The process of claim 19, wherein the solvent is toluene.

21. The process of claim 12, wherein the first acid is selected from the group consisting of mineral acids, hydrogen sulfate salts, trifluoroacetic acid, formic acid, hydrobromic acid, acetic acid and formic acid.

22. The process of claim 21, wherein the first acid in step a is hydrochloric acid.

23. The process of claim 12, wherein the second acid in step c is acetic acid.

24. The process of claim 12, wherein the mixture in step b is cooled to a temperature of between about -15 and about 15°C.

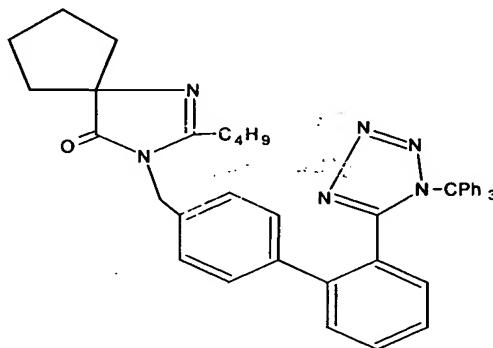
25. The process of claim 24, wherein said mixture is cooled to about 0°C.

5 26. The process of claim 12, wherein the combination in step d is heated to reflux for between about 2 and about 10 hours.

27. The process of claim 12, wherein the base used in step e is NaHCO₃.

28. The process of claim 12, wherein the compound of structure I is recovered by filtration and evaporation under reduced pressure.

10 29. A process of making a compound of structure I



comprising the steps of:

a) combining a valeramide derivative with 2,6-lutidine and oxalyl chloride in the presence of an organic solvent;

15 b) cooling the combination;

c) maintaining the combination for between 0.25 and 4 hours, whereby an inidoyl chloride intermediate is formed;

d) further combining an amine and an organic solvent with the combination;

e) heating the resulting combination to reflux for about 0.1 to about 1 hours;

20 f) thereafter contacting the mixture with a base whereby two phases are obtained;

- g) separating the phases obtained; and
- h) recovering the compound of structure I.

30. The process of claim 29, wherein the valeramide derivative is selected from the group consisting of cyclopentyl valeramide and 5-(4'methylvaleramide-biphenyl-2-yl)-1-trityl-1H-tetrazole.

5

31. The process of claim 29, wherein the organic solvent is toluene.

32. The process of claim 29, wherein the combination of step b is cooled to a temperature of between about -15 and about 15°C.

33. The process of claim 32, wherein the combination is cooled to about 0°C.

10

34. The process of claim 29, wherein the amine is selected from the group consisting of 5'-(4'aminomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole and 1-aminocyclopentane carboxylic acid ethyl ester.

35. A process for making irbesartan comprising the steps of:

15

- a) reacting 1-(N'-pentanoylamino)cyclopentanecarboxylic acid amide with 5-(4'-bromomethylbiphenyl-2-yl)-1-trityl-1H-tetrazole in the presence of a base, a solvent and a phase transfer catalyst;
- b) combining water with the reaction mixture, whereby two phases are obtained;
- c) separating the two phases obtained; and
- d) recovering 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-yl] methyl]-20 1,3-diazaspiro[4.4]non-1-ene-4-one; and
- e) converting the product of step d to irbesartan.

36. A process for making irbesartan comprising the steps of:

25

- a) reacting a valerimidate derivative with a first amine in the presence of an acid and an organic solvent;
- b) maintaining the mixture for between 6 and 24 hours;
- c) cooling the mixture;
- d) adding a second amine and a catalytic amount of an acid to the mixture;

- e) heating to reflux;
- f) maintaining the mixture for between 2 and 24 hours;
- g) neutralizing the mixture with a base;
- h) separating the phases obtained; and
- 5 i) recovering 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-yl] methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one; and
- j) converting the product of step i to irbesartan.

37. A process for making irbesartan comprising the steps of:

- a) reacting a valeramide derivative with 2,6-lutidine and oxalyl chloride in the presence of an organic solvent;
- 10 b) cooling the mixture;
- c) maintaining the mixture for between 0.25 and 4 hours;
- d) adding an amine and an organic solvent to the mixture;
- e) heating to reflux;
- 15 f) maintaining the mixture for between 0.1 and 1 hours;
- g) neutralizing the mixture with a base;
- h) separating the phases obtained; and
- i) recovering 2-butyl-3-[[2'-(1-trityl-1H-tetrazol-5-yl)-biphenyl-4-yl] methyl]-1,3-diazaspiro[4.4]non-1-ene-4-one; and
- j) converting the product of step i to irbesartan.

20 38. 1-(1'-ethoxy)pentanaminylcyclopentane carboxylate.

39. 4'-pentanaminyl-2-(1-trityl-1H-tetrazol-5-yl)biphenyl.

40. In a process for making irbesartan, the step of reacting 4'-aminomethyl-2-(1-trityl-1H-tetrazol-5-yl)biphenyl with a salt of ethyl valerimidate to form 4'-[((1-ethoxy)pentanaminyl)methyl]-2-(1H-tetrazol-5-yl)biphenyl.

41. The process of claim 31 further comprising the step of reacting 4'-(1-ethoxy)pentanaminyl)methyl-2-(1H-tetrazol-5-yl)biphenyl with ethyl 1-aminocyclopentane carboxylate.

5 42. In a process for making irbesartan, the step of reacting 4'-aminomethyl-2-(1-trityl-1H-tetrazol-5-yl)biphenyl with ethyl 1-(1'-ethoxy)pentanaminylcyclopentane carboxylate.

10 43. In a process for making irbesartan, the step of reacting 4'-aminomethyl-2-(1-trityl-1H-tetrazol-5-yl)biphenyl with ethyl 1-(N-valeroylamino)cyclopentane carboxylate in the presence of oxaloyl chloride and a base scavenger.

44. The process of claim 34 wherein the scavenger is 2,6-lutidine.

15 45. In a process for making irbesartan, the step of reacting ethyl 1-amino-1-cyclopentanecarboxylate with a valerimidate derivative.

46. The process of claim 36 wherein the valerimidate derivative is the methanesulfonic acid salt of ethyl valerimidate.